DOI:
10.1111/odi.13083

Document Version
Peer reviewed version

Title

WWOM VII: A systematic review of immunobiologic therapy for oral manifestations of pemphigoid and pemphigus

Running title

WWOM VII: Biologics in pemphigoid and pemphigus

Keywords:
mucous membrane pemphigoid, pemphigus vulgaris, blistering disease, biologic agents, rituximab, autoimmunity

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Abstract

Objective. To assess the evidence for treatment of oral involvement of pemphigus and pemphigoid with biologics.

Study Design. This systematic review used a comprehensive search strategy to identify literature describing oral involvement of pemphigus or pemphigoid treated with a biologic agent. The primary outcome measures were efficacy and safety of biologic therapy.

Results. Inclusion criteria was met by 154 studies including over 1200 patients. Treatment of pemphigus with a total of 11 unique biologic agents and 3 unique combinations of agents is reported. Five randomized controlled trials (RCT) were included in the final analysis that investigated infliximab, IVIg, rituximab and autologous platelet-rich plasma therapy for pemphigus vulgaris. Three non-RCT studies reported on successful rituximab or IVIg therapy for mucous membrane pemphigoid. Studies demonstrated considerable heterogeneity in agent, methods, and quality.

Conclusions. Evidence clearly describing oral tissue response to biologic therapy is sparse. Two RCTs support use of rituximab, one supports use of IVIg, and one pilot study suggests intralesional injection of autologous platelet-rich plasma aids healing of oral PV lesions. As oral lesions of pemphigus and pemphigoid can be refractory to systemic therapy, drug trials including biologic therapies should document details regarding response of the oral lesions to therapy.

Introduction

Biologics have gained recognition as promising therapies for inflammatory and autoimmune disorders, and there is significant interest in evaluating the potential of this drug class for the treatment of complex oral disease. A biologic or biologic therapy is defined as a substance that is made from a living organism or its products to treat disease (NCI Cancer Dictionary). Strides have been made in the treatment of the autoimmune epidermal blistering disease pemphigus using biologics, and the United States Food and Drug Administration (FDA) approved the use of a biologic agent, rituximab, for the treatment of adults with moderate to severe pemphigus vulgaris (PV) in June 2018.

Pemphigus consists of a group of autoimmune diseases characterized by epithelial blistering affecting cutaneous and/or mucosal surfaces. Intraepithelial blister formation results from the loss of adhesion of keratinocytes (acantholysis), with immunoglobulin G (IgG) antibodies directed against desmosomal proteins. PV is the most common and most aggressive variant (Baum et al., 2016). The oral mucosa is the site of initial presentation in 50-75% of cases (Mustafa, Porter, Smoller, & Sitaru, 2015; Robinson, Lozada-Nur, & Frieden, 1997; Shamim, Varghese, Shameena, & Sudha, 2007).

The complex pathogenesis of PV involves the generation of autoantibodies against connective proteins of the skin and mucosa including desmosomal cadherins (Saito et al., 2012). Desmoglein 3 is the major antigen, but 50–60% of patients also have anti-desmoglein 1 antibodies (Cozzani et al., 2013; Kasperkiewicz et al., 2017). The clear role of autoantibodies in PV pathogenesis suggests an important therapeutic role for targeted agents that block the generation or survival of autoreactive immune components (Ellebrecht & Payne, 2017).

The mainstay of treatment of pemphigus is immunosuppressive therapy (Ahmed, 2001, 2007). Management consists of two main phases: induction of remission and maintenance of remission. For decades, systemic corticosteroids have been the therapy of choice for induction with maintenance

effected by azathioprine, mycophenolate mofetil, dapsone, methotrexate, cyclophosphamide, gold, and cyclosporine. Adjuvant techniques to reduce antibody load include plasmapheresis, and immunoadsorption (McMillan et al., 2015). Mucocutaneous PV tends to be a more severe disease, with oral lesions being slower to respond to treatment and less likely to achieve remission off-treatment than solely cutaneous disease(Kavusi et al., 2008). There have been recent international attempts to standardize the diagnosis and management of pemphigus, and newer therapies such as biologics or intravenous immunoglobulin (IVIg) therapy may offer significant advantages over systemic corticosteroids (Ellebrecht & Payne, 2017; Hertl et al., 2015; D. F. Murrell et al., 2018).

Mucous membrane pemphigoid (MMP) is a rare, predominantly mucosal subepithelial blistering disorder involving the oral mucosa, conjunctiva, anogenital tissues, and upper aerodigestive tract. Wide variation in disease severity ranges from minimal painless oral involvement to severe blistering with scarring sequelae. Several basement membrane proteins are associated with autoantibody reactivity including BP180, BP230, both subunits of α6β4 integrin, laminin 332, and type VII collagen(Enno Schmidt & Zillikens, 2013). Mild disease is managed with topical steroids and moderate/severe disease with short-term prednisone and long-term mycophenolate mofetil, azathioprine or dapsone (Taylor et al., 2015).

Based upon the rationale that pemphigus and mucous membrane pemphigoid are primarily autoantibody-driven autoimmune disorders, therapies that deplete autoreactive B cells have been investigated for the treatment of these disorders (Nagel, Hertl, & Eming, 2009). Rituximab is a chimeric murine–human monoclonal antibody of the IgG1 subclass, directed against the B-lymphocyte-specific antigen CD20, expressed by early B cells in the bone marrow, autoantigen-specific B cells, memory B cells and mature B cells (Nagel et al., 2009). Rituximab was first used to treat PV in the early 2000s in patients refractory to conventional treatment. By 2007, several case series had emerged showing efficacy (Ahmed,

Spigelman, Cavacini, & Posner, 2006; Joly et al., 2007; E. Schmidt, Seitz, Benoit, Brocker, & Goebeler, 2007). Following treatment with rituximab there is rapid and sustained (6–12 months) depletion of circulating and tissue-based B cells. Initial studies for dosing for rituximab in immunobullous disorders reflected a regimen derived from the treatment of patients with lymphoma, using four weekly infusions of 375mg/m^2 (Joly et al., 2007). Since then, clinicians have adopted an alternate regimen: two infusions of 1000mg separated by two weeks (Y. A. Leshem et al., 2014; Yael A. Leshem, Hodak, David, Anhalt, & Mimouni, 2013). Advantages of this regimen include fewer infusions and a lower total dose of rituximab. Less data is available for rituximab use in MMP.

The Seventh World Workshop in Oral Medicine sponsored this systematic review to evaluate the efficacy of biologic therapies in the management of pemphigus, including subtypes PV and Paraneoplastic pemphigus (PNP), and MMP involving the oral mucosa, with or without cutaneous lesions. The study summarizes the evidence supporting the use of biologics as first line, second line or adjuvant therapy in these conditions. This review also highlights the wide variation in clinical practice and the need for high-quality research to validate current guidelines and to explore future therapies.

Methods

A systematic review was conducted following a detailed protocol. Key aspects of the protocol are summarised here.

Inclusion Criteria

Randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies (e.g., cohort studies, case series and case reports) were included. Studies investigating biologic treatments for PV, PNP and MMP with oral involvement were included. Case reports, case series, meeting abstracts and clinical

observations were included only if there was a clear description of biologic therapy for patients with oral disease.

Data from study participants were included if accepted criteria in all three diagnostic domains: clinical presentation, histology, and immunofluorescence was met and there was evidence of oral mucosal involvement and assessment.

Exclusion criteria

Studies describing only cutaneous disease, those that reported primarily on cancer therapy, papers with insufficient information about oral manifestations of disease or oral tissue response to therapy, non-English papers, and full text unavailable papers were excluded. For duplicate reports or datasets identified, only the most final version of the paper was included. Some studies included in the final dataset included a mixed disease cohort. Participants with cutaneous disease only or involvement at only non-oral sites were excluded from data extraction when individual patient response data were available.

Types of interventions

Active biologic treatment included any preventive, palliative, or curative intervention administered systemically aimed at the treatment of PV, PNP and MMP meeting the United States National Institutes of Health, National Cancer Institute definition of a biologic or biologic therapy: a substance that is made from a living organism or its products to treat disease.

Types of outcome measures

Primary outcome measures were efficacy and safety. Secondary outcome measures included time to disease control, time to disease relapse, disease severity score, serum antibody titers, and quality of life.

Electronic searches

Assisted by a research librarian (RP), MEDLINE® (via PubMed), Embase, Scopus and the Cochrane Library from date of database inception through October 26, 2018 were searched using general terms for

biologics, or terms for specific drugs or drug classes combined with terms for pemphigus, pemphigoid, or other related diseases. Either medical subject headings (MeSH) or Embase subject headings (Emtree) where available and keywords when applicable were used. Conference papers were searched in Embase and Scopus. The electronic search excluded all non-English language papers which did not have an English version. This study was structured according to PRISMA statement for reporting of systematic review and meta-analysis.

Searching other resources

We reviewed the bibliographies of RCTs and review articles and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTTRP) (apps.who.int/trialsearch/)) to identify additional published or unpublished data. We did not contact investigators or study sponsors. The detailed search strategy is provided in the online Supplementary Material Appendix 1.

Selection of studies

Abstracts of each search-identified study were evaluated by two authors who reached agreement for inclusion. Studies that clearly did not satisfy the inclusion criteria were eliminated, and full copies of the remaining studies were obtained. Two review authors (BPC, JWM) read the studies independently and reached agreement by discussion. Studies were not anonymized before assessment. Study tracking through the selection process was completed using Covidence systematic review software ("Covidence systematic review software,"). The flow of studies is illustrated in a PRISMA flow chart (Liberati et al., 2009).

Data extraction and management

One review author (BPC or JWM) extracted data independently, using a standard custom data extraction form for full studies (online Supplementary Material Appendix 2) and a short data extraction form for case reports and case series (online Supplementary Material Appendix 2) through Google Forms which concatenated results into a database. Forms were based on STROBE criteria (von Elm et al., 2008). Data extraction was cross-checked by the other author against the full manuscript.

Assessment of risk of bias in included studies

Two review authors (BPC, JWM) independently assessed then cross-checked and discussed the assessment of risk of bias for each RCT (n=5). The revised Cochrane tool to assess risk of bias in randomized trials (RoB 2) for individually-randomized, parallel-group trials (October 2018) was used to assess the RCTs across five domains: 1. Bias arising from the randomization process; 2. Bias due to deviations from intended interventions; 3.Bias due to missing outcome data; 4. Bias in measurement of the outcome; and 5. Bias in selection of the reported result (Higgins JPT). Risk of bias for each domain was assessed as “high,” “low,” or “some concerns.” A study with one or more “high” risk of bias judgments for any given domain was deemed overall to have a high risk of bias.

Data synthesis and measures of treatment effect

Case reports and series were scored to evaluate the question, ”Was the therapy effective in managing the oral disease?” the outcomes of each study were categorized by reviewers during data extraction on a 4-point scale: Completely Effective (in all patients), Mostly Effective in more than 50% of patients (not totally effective), Partially Effective (in less than 50% of patients treated with biologics--this option selected if data were unclear about %, but drug was not effective in all patients), or Ineffective in all patients. Effectiveness was based on the outcome criterion within the individual study. The category was assigned by one reviewer and confirmed by a second, and any disparity was settled through discussion. Studies

that included multiple types of pemphigus or pemphigoid diagnoses were excluded from this overview analysis, which limited the categorical summary to case reports and case series, as all other study types had mixed disease cohorts. The results are reported as percent of total reports for that drug and disease category.

Results

From 6416 unique records, we identified 165 studies including more than 1200 patients with oral involvement of pemphigus or pemphigoid treated with a biologic agent. Due to the emerging nature of this field, case reports and case series were included in this review and comprised 80% of the number of total publications and 47% of the overall patients (Figure 1). The remaining 29 full studies were comprised of 5 randomized controlled trials, and 24 non-randomized studies (3 non-randomized controlled trials, 14 cohort studies, and 7 non-controlled trials). Specific biologic agent and dosing varied across studies and was variably reported. Studies included 11 unique biologic agents and 3 combination therapies. The breakdown of publication type by biologic therapy is shown in Figure 1b. MMP or PNP was not the topic of any identified RCTs. Most (135/154, 88%) of the included studies used biologics as salvage therapy in heavily-treated patients who were refractory to other modalities.

Detailed analysis of the 5 RCTs for the treatment of pemphigus are summarized below and in Table 1. Four studies were classified as parallel RCTs (Joly 2017, Hall 2015, Kanwar 2014, Amagai 2009) and one was a 'split-mouth' RCT (El-Komy 2018). Three of the studies were multicenter (Joly 2017, Hall 2015, Amagai 2009). Two of the RCTs used placebo controls (Hall 2015, Amagai 2009) but allowed both groups to continue some form of active pharmaceutical intervention (i.e. systemic steroids). All the RCTS used clinical outcome measures, however, there was considerable heterogeneity in the specific outcome measures employed. Reduced dosage of corticosteroids and PV antibody titers were used as surrogate markers for treatment efficacy in several studies. Because of the heterogeneity of outcomes for each of the studied interventions, quantitative meta-analysis could not be conducted. Analyses of the relevant

outcomes (relative risks and 95% CIs) from the RCTs are summarized in detail below. A quality assessment of included randomized controlled trials was performed using Cochrane Risk of Bias (RoB 2.0) and is detailed in Supplemental Figure 1.

Rituximab was tested in 2 RCTs that included assessment of the oral mucosa. Kanwar *et. al.* conducted randomized comparative observer-blinded pilot study that compared two rituximab dosing regimens for the treatment pemphigus (Kanwar et al., 2014). Patients with active PV (n=15) or PF (n=7) who were treatment-naive, resistant to previous therapies, or who had severe disease were recruited from a dermatology department in a tertiary care setting in India. They were randomized to receive either two doses of 500 or 1000 mg rituximab at an interval of 15 days and were followed for 48 weeks. The primary endpoint was clinical efficacy between treatments in terms of early (time to disease control and time to complete consolidation phase) and late end points [partial response (PR) and complete response, (CR)] on the Ikeda severity score scale as assessed by an examiner blinded to treatment group (Ikeda et al., 2003). No significant adverse events (SAEs) were recorded in either group, though AEs including mild infusion reactions, upper respiratory tract infections, diarrhea, striae and acneiform eruptions were seen in both groups. The mean number of AEs was 1.36 in the 2x500 mg group and 1.45 in the 2x1000 mg group. At week 40, the fall in Ikeda severity score was steeper in the 2x1000 mg group than in 2x500 mg group ($P = 0.049$). Patients in the 2x500 mg group received a significantly higher cumulative dose of azathioprine ($P = 0.018$). ELISA indices of Dsg1 and Dsg3 showed a statistically significant decline in the 2x1000 mg group only, and B cell repopulation occurred earlier 8 weeks earlier in the 2x500 mg group.

In 2017, Joly and colleagues published results from an open-label multicenter parallel RCT comparing oral prednisone alone versus rituximab and a short-term prednisone regimen to treat newly-diagnosed pemphigus (Joly et al., 2017). Pemphigus patients with PV (n=74) or PF (n=16) were recruited at 25 centers in France and randomized to one of 2 groups: oral prednisone alone starting at 1.0 or 1.5 mg/kg/day, tapered over 12-18 months (n=44) , or 1000 mg intravenous rituximab on days 0 and 14, and

a 500 mg dose at months 12 and 18 combined with a short-term prednisone treatment of 1.0-1.5mg/kg/day tapered over 3-6 months (n=46). Stratification by severity of pemphigus was included in the randomization matrix, and moderate-to-severe pemphigus was defined as skin involvement of greater than 5% body surface area, or significant mucosal involvement defined as more than ten mucosal erosions, or diffuse gingivitis or confluent large erosions, or involvement of two or more mucosal sites. Scoring of the oral mucosa was incorporated into the mucous membrane subsection of the Pemphigus Disease Area Index (PDAI) scoring tool, however, oral tissue subscores were not reported for this study (Dedee F. Murrell et al., 2008). Patients assigned to rituximab plus short-term prednisone had significantly fewer SAEs (mean 0·59 [SD 1.15]) than patients those assigned to prednisone alone (mean 1.20 [SD 1·25]), which was attributed to the lower cumulative steroid dose in the rituximab group. At the primary endpoint, month 24, 41 (89%) of 46 patients assigned to rituximab plus short-term prednisone were in complete remission off-therapy versus 15 (34%) of 44 assigned to prednisone alone ($p<0·0001$). The corresponding relative risk of success of is 2.61 (95% CI 1·71–3·99, $p<0·0001$). Data from this study demonstrate a clear benefit of rituximab as a first-line therapy for pemphigus patients, including those with severe oral mucosal manifestations.

Inflammation is a significant factor in the feed-forward circuit of autoimmune disease. Tumor necrosis factor alpha (TNF-α) is cytokine that has been detected in the skin lesions of patients with PV, and serum levels of TNF-α have been correlated with disease activity. In 2015, Hall *et al.* reported treatment of pemphigus patients using infliximab, an inhibitor of TNF-α (Hall et al., 2015). This double-blinded, placebo-controlled trial was carried out at 6 centers in the United States. Ten patients received infusions of infliximab (5 mg kg) at weeks 0, 2, 6 and 14 while receiving standard-of-care with follow-up at weeks 10, 18, 22 and 26. Ten control group patients received infusions of placebo at weeks 0, 2, 6 and 14 while receiving prednisone with follow-up at weeks 10, 18, 22 and 26. To qualify for the study, patients were required to score moderate or severe on both the mucosal and cutaneous subsections of a disease

activity score. For the mucosal subsection, a moderate score required 6–10 lesions/small ulcers. This scale was used for clinical scoring at each study visit. In this trial, the primary endpoint was defined as response to treatment at week 18. Subjects were responders if they achieved a prednisone dosage ≤ 25% of the initial starting dose or ≤ 10 mg daily and had no new blisters within the previous 4 weeks. Groups did not differ in AE incidence, and no infectious complications of Grade 3 or greater (Common Terminology Criteria for Adverse Events, CTCAE 3.0) were reported (Trotti et al., 2003). At the primary endpoint, week 18, one subject in each group had responded. At week 26, three infliximab-treated subjects versus none in the placebo group had responded. Assessment of IgG anti-Dsg1 and anti-Dsg3 antibody titers found significantly lower levels in infliximab-treated patients at week 18 and 26. Study authors concluded that infliximab therapy was not shown to be clinically effective for the treatment of patients with PV.

Intravenous immunoglobulin (IVIg) is used as an adjuvant steroid sparing agent in PV or as a monotherapy. It is a purified product consisting mostly of IgG molecules made from a pool of donors and is thought to have multiple mechanisms of action including downregulation of antibody production by plasma cells (Hartung, 2008). Amagai and colleagues conducted a three-arm clinical trial to test two doses of IVIg versus placebo using a new outcome measure, time to escape protocol (length of time participant stayed on protocol without requiring additional treatment up to day 85, TEP) (Amagai et al., 2009). Pemphigus patients, including PV (n=40) and PF (n=21), received a 200mg IVIg, 400mg IVIg, or placebo infusion administered in divided doses over 5 days plus oral steroids. TEP was the primary endpoint of the study. Secondary endpoints included change in pemphigus activity score (PAS) which specifically scores oral mucosal and skin lesions. At day 85, AEs, called adverse drug reactions in this study, occurred in 29% of the 400mg group, 35% of the 200mg group and 25% of the placebo group, with no statistical differences between groups. By day 85, 11/20 patients on placebo required elevated treatment (escape), 4/20 patients in the 200mg IVIg group escaped after 10+ days, and 2/21 patients on 400mg IVIg escaped after 22+ days. A log-rank test was used to compare treatment groups to placebo only and found a significant

change in TEP between placebo and the 400mg group ($p<0.001$). The PAS, which included mucosal scoring, was significantly changed (decreased) from baseline at all time-points in the 400mg group, after day 15 only in the 200mg group, and not significantly changed in the placebo group. Similarly, anti-Dsg1 and Dsg3 IgG titers were decreased at day 43 and 85 in the 400mg group, at day 85 only in the 200mg group, and not at all in the placebo group.

Direct therapy may be applied to isolated oral lesions or those refractory to systemic treatment. Autologous platelet-rich plasma (PRP) has been used locally to accelerate cutaneous and oral wound healing, and to treat refractory oral ulcers in autoimmune conditions (Bojanic et al., 2018; Lacci & Dardik, 2010). In 2018, El-Komy *et. al.* reported a pilot single center randomized double-blind study comparing local injection of PRP on one side of the mouth with active standard treatment: local injection of triamcinolone acetonide on the contralateral side (El-Komy, Saleh, & Saleh, 2018). The trial was conducted in an Egyptian hospital in 11 PV patients with oral pain or oral lesions. Buccal mucosa or gingiva was injected every 14 days for 3 months with 1 milliliter of autologous PRP at the base and side of the erosion, and on the opposite side with 10 mg/ml triamcinolone. Patient and scoring physician were blinded to the treatment assignment. Scoring was completed per the oral PDAI for the primary endpoint of oral lesion improvement after 90 days. No AE summary was provided for the study. Nine patients completed the study, and triamcinolone injection decreased the mean oral PDAI from 2.3 to 0.9, and PDAI scores after PRP injection moved from 2.6 to 1.0. Statistically equivalent clinical improvement was measured when refractory oral ulcers of PV were injected with either steroid or PRP.

MMP patients were included in 1 non-randomized controlled trial and 2 cohort studies that used IVIg treatment, 2 cohort studies that examined rituximab treatment (Table 1). Sami *et. al.* reported on 7 severe oral pemphigoid patients treated with IVIg therapy versus 7 similar patients on standard therapy (N. Sami, Bhol, & Ahmed, 2002). The primary outcome was change in the anti-human alpha6 integrin antibody titers, which have a pathophysiologic role in blister formation in OP. Titers in the IVIg group

dropped at a similar rate to controls through month 4 of treatment, but then declined at a significantly faster rate after six months of treatment (P = 0.03). A case series that examined patients with autoimmune mucocutaneous blistering diseases on monthly courses of IVIg included 4 MMP patients (Segura et al., 2007). One had a complete clinical response, 2 had a partial response and 1 did not respond to treatment. Steroid refractory MMP patients (n=15) were treated with IVIg in a separate non-controlled study (Naveed Sami, Bhol, & Razzaque Ahmed, 2002). All (15/15) patients had effective clinical response and were able to discontinue previous systemic therapies, with no reported AEs. Salvage therapy with rituximab has been reported in 4 patients across 2 case series that included MMP patients (Kolesnik et al., 2014; E. Schmidt, Seitz, Benoit, Bröcker, & Goebeler, 2007). One patient had clinical progression of MMP (51) on rituximab combined with immunoadsorption, 2 patients achieved a complete response (reduction in dose of systemic immunosuppression) after several (number varied) rituximab infusions, and 1 patient had a partial response.

Scoring of the case reports and case series in the dataset was done to answer, "was the therapy effective in managing oral disease?" Results of each study were categorized as: Completely Effective (in all patients), Mostly Effective in more than 50% of patients (not totally effective), Partially Effective (in less than 50% of patients treated) or Ineffective in all patients. In the case studies and series using rituximab in pemphigus vulgaris with oral involvement (n=48), rituximab was Completely Effective in managing oral disease in 40% of cases and Mostly Effective in 48% of cases. It was Partially Effective or Ineffective in 6% each of case reports or series. For MMP (n=11), rituximab was Completely Effective in 45% of cases, Mostly Effective in 27% of cases and Partially Effective in 27% of cases. A wider response distribution is noted in cases of PNP treated with rituximab (n=14), in which 29% of cases were Completely Effective, 21% of cases were Mostly Effective, 21% were Partially Effective, and rituximab was Ineffective for PNP in 29% of cases. IVIg was reported to be Completely Effective for treatment of MMP in all case

reports or series (n=6). For PV (n=11), IVIg was Completely Effective in 9% of cases, Mostly Effective in 64% of cases, Partially Effective in 18% of cases and Ineffective in 9% of cases.

Discussion

In this systematic review, we assess the evidence base for treating oral manifestations of pemphigus and pemphigoid with biologics. The literature which clearly describes response to biologic therapy in the oral tissues affected by pemphigus and pemphigoid is sparse, and randomized controlled studies are thus far limited to the treatment of pemphigus. Five RCTs were identified by the search parameters, along with 24 other non-controlled or non-randomized studies using biologic agents to treat pemphigus or pemphigoid. Two RCTs support use of rituximab to reduce total cumulative corticosteroid dose and associated side effects. One trial that included heterogenous group of new-onset and refractory patients found that higher doses of rituximab (two doses of 1000 mg at a 15-day interval) were more effective. A second RCT treated new-onset PV patients only with a modified rituximab regimen of 1000 mg on days 0 and 14, and 500 mg at months 12 and 18 along with a steroid pulse, and at 24-months on study, 89% of rituximab-treated patients were in full remission (off therapy) while only 34% of steroid-only-treated patients were off therapy for pemphigus. Unfortunately, limited specific information was available from these trials regarding oral mucosal response to rituximab therapy. The trial of IVIg included patients with moderate-severe oral mucosal lesions and found that 400mg doses of IVIg were superior to placebo in preventing pemphigus flares requiring escalated therapy. Finally, one small pilot study suggests that intralesional injection of autologous platelet-rich plasma may aid in healing of oral PV lesions when intralesional steroids are contraindicated, equivalent to triamcinolone acetonide injection, however significant concerns exist with the small size and design of this study – specifically that agents given on one side of the mouth may have affected lesions on the contralateral side. Results of infliximab therapy for pemphigus found that it neither reduced systemic prednisone dosage required nor reduced occurrence of new lesions. The four agents investigated in RCTs: rituximab, infliximab, IVIg, and PRP had

equivalent safety profiles to that of control agents, generally standard-of-care steroid regimens, in the studies.

Any analysis of the case reports and case series included in this literature survey is inherently biased and should be interpreted with caution, as single case studies are rarely published to report treatment failures. IVIg and rituximab are the most reported agents in these papers, and those agents have been tested in some form of RCT for pemphigus. They have performed well, but with lower success rates than suggested by the case reports/series descriptive analysis.

Data from the Joly 2017 study was the basis for the United States FDA approval of the use of rituximab for the treatment of adults with moderate to severe pemphigus vulgaris (PV) in mid-2018. Additional trials are in progress and it is anticipated that treatment of PV with rituximab will soon be better described in the literature.

New targeted therapeutic agents are in development for treatment of pemphigus that could further limit side-effects through more precise targeting of autoimmune pathobiology. These include chimeric antigen receptor therapy to target anti-desmoglein-3-specific B cells that produce pathogenic pemphigus autoantibodies (Ellebrecht et al., 2016), blockade of T-cell co-receptors such as CD154 that are required by B cells for stimulation of autoantibody production, and a Bruton's tyrosine kinase (BTK) inhibitor that is in active clinical trials for PV (Principia Biopharma, 1993–2018), among other promising strategies.

Another emerging nuance of this field that is beyond the scope of this review are the reports of oral bullous lesions induced by biologic therapies (Naidoo et al., 2016; Vigarios, Epstein, & Sibaud, 2017). These may occur after checkpoint inhibitor or other biologic therapy for myriad conditions and can present with a standard serologic and histologic profile of pemphigus or pemphigoid. These cases are

typically addressed with interruption of biologic therapy and initiation of systemic and topical steroids but may need differential clinical management versus non-drug-induced bullous disease.

Oral lesions of pemphigus and pemphigoid can be refractory to systemic therapy, and in this emerging drug class, it is critical to report on the timing and response of the oral cavity to biologic therapy from clinical trials to aid in the clinical decision-making process for patients with severe or primarily oral manifestations of bullous disease. Evidence is missing from the literature that could guide earlier recommendations for biologic therapy to address problematic oral manifestations. Given the challenges of treating these conditions, it would be helpful for future RCTs and case-control studies to (1) include an oral-specific scale or report on oral mucosal outcomes that are often scored as part of comprehensive scales such as the PDAI and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), (2) track and report timing of disease resolution at specific sites (oral vs ocular vs skin), (3) describe site-specific symptoms including oral symptoms and the timing of response of these to biologic (or other) therapies, (4) include patient-reported outcomes tracking better or worse control of pain and discomfort at mucosal sites and tolerance of biologics versus traditional therapies.

Conflicts of Interest: ASP holds equity in Cabaletta Bio, focused on targeted therapy of autoimmune diseases including pemphigus, and is an inventor on patents licensed by Novartis and Cabaletta Bio for autoimmunity.

Acknowledgements

The authors gratefully acknowledge the following organizations and companies that provided financial support for WWOM VII: American Academy of Oral Medicine, European Association of Oral Medicine, The British Society for Oral Medicine, The National Institute of Dental and Craniofacial Research, Colgate-Palmolive, Henry Schein Cares Foundation, AFYX, Unilever, Xerostom, Oral Diseases, and The World Dental Education Foundation. JWM is supported by the Intramural Research Program of the NIH, NIDCR.

In addition, the authors express their sincere appreciation for the opportunity to collaborate with the WWOM VII Steering Committee. This committee provided the conceptual framework and logistical support to produce the WWOM VII Conference in September 2018 in Gothenburg, Sweden. In addition, the Steering Committee provided scientific and editorial critiques of this manuscript. The entire Steering Committee is listed below, in alphabetical order: Martin S. Greenberg (USA), Timothy A. Hodgson (UK), Siri Beier Jensen (Denmark), A. Ross Kerr (USA), Peter B. Lockhart (USA), Giovanni Lodi (Italy), Douglas E. Peterson (USA).

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571 Table 1

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Study	Year	Intervention	Country	Study Type	No of sites	No of patients	Sex, M:F	Age (yr)	Disease	Disease Status	Disease Duration (mean)	Biologic Dose	Adverse Effects
Joly et al	2017	Rituximab	France	RCT	25	90	40;50	53.3	Pemphigus vulgaris, pemphigus foliaceus	Initial	97.8 days	1000mg day 1 and 14, then 500mg at 12m and 18m	Headache, asthenia, fever, chills, nausea, septicemia, pyelonephritis, death
Hall et al	2015	Infliximab	USA	RCT	6	20	12;8	53.25	Pemphigus vulgaris	Refractory	Not stated	5mg/kg at weeks 0, 2, 6 and 14	No infectious complications
Kanwar et al	2014	Rituximab	India	RCT	1	22	11;11	33.4	Pemphigus vulgaris, pemphigus foliaceus and pemphigus erythematosus	Refractory	20.2 months	500mg or 1000mg, two doses, 2 weeks apart	Infusion reactions, upper respiratory tract infections, diarrhoea, stria, acneiform eruptions
Amagai et al	2009	IVIG	Japan	RCT	27	61	27;34	53.36	Pemphigus vulgaris, pemphigus foliaceus	Refractory	24.4 months	200mg or 400mg/kg/d, divided over 5 consecutive days	Headache, aggravated chronic hepatitis C, decreased lymphocytes, palpitations, abdominal discomfort, constipation, nausea, pain at the injection site, increased creatinine, increased blood pressure, decreased platelet count, hepatic dysfunction, common cold, muscle pain.
El-Komy et al	2018	Platelet rich plasma	Egypt	Split-mouth RCT	1	11	4;7	41.1	Pemphigus vulgaris	Refractory	4mo - 8 years	1ml intralesional PRP every 14 days for 3 months	None
Kolesnik et al	2014	Rituximab	Germany	Cohort	1	3	2;1	68.7	Mucous membrane pemphigoid	2 refractory, 1 no prior treatment	35.3 months	375 mg/m² at weekly intervals x 4	Infection in 1 case
Schmidt et al	2007	Rituximab	Germany	Cohort	1	1	M=1	78	Mucous membrane	Refractory	64 months	375mg/m2 at weekly intervals x 4	None

									pemphigoid				
Segura et al	2007	IVIG	Spain	Cohort	1	4	3 female, 1 not defined	70.8	Mucous membrane pemphigoid	Refractory	88.5 months	2 g/kg/cycle over 4 or 5 consecutive days	Cephalea, hypertension, epitaxis, headache, fever, N+V+D
Sami et al	2002	IVIG	USA	Non-randomised trial	1	7	2;5	55.5	Mucous membrane pemphigoid	Contraindication to immunosuppressive therapy	Not stated	1–2 g/kg/cycle infused over 3 consecutive days	None
Sami et al	2002	IVIG	USA	Cohort	1	15	7;8	66	Mucous membrane pemphigoid	Refractory	Not stated	1–2 g/kg/cycle infused over 3 consecutive days	No side effects reported

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